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Protocol for Study M16-763

Indication: ABBV-105, Given Alone or in Combination with Upadacitinib (ABBV-599), in Adult Subjects with Active Rheumatoid Arthritis Who Have Completed a Preceding Phase 2 Randomized Controlled Trial

VERSION:	4.0	DATE:	06 February 2020
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FULL TITLE: A Phase 2, Multicenter, Double-Blind, Parallel Group Long Term Extension Study in Rheumatoid Arthritis Subjects Who Have Completed a Preceding Phase 2 Randomized Controlled Trial with ABBV-105 Given Alone or in Combination with Upadacitinib (ABBV-599)

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PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

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1 SYNOPSIS

Title: A Phase 2, Multicenter, Double-Blind, Parallel Group Long Term Extension Study in Rheumatoid Arthritis Subjects Who Have Completed a Preceding Phase 2 Randomized Controlled Trial with ABBV-105 Given Alone or in Combination with Upadacitinib (ABBV-599)	
Background and Rationale:	This study will provide data on the long-term safety, tolerability, and efficacy of ABBV-105 and ABBV-599 in rheumatoid arthritis (RA) subjects who have completed the Phase 2 study of these compounds (Study M16-063). ABBV-105 is a novel, covalent Bruton's tyrosine kinase (Btk) inhibitor being developed for the treatment of immune-mediated inflammatory diseases including RA. ABBV-105 may be given alone or in combination with upadacitinib, which is known as ABBV-599. Upadacitinib is a novel Janus kinase (JAK) inhibitor, which displays unique selectivity for the JAK1 receptor. ABBV-105 and ABBV-599 should be effective in decreasing signs and symptoms associated with active RA in patients with inadequate response or intolerance to biologic disease-modifying antirheumatic drugs (bDMARDs) by interfering with the JAK1/Btk pathways. Concurrent inhibition of JAK1/Btk pathways in RA may increase percent of those responding, as well as depth of response (relative to inhibiting either pathway alone), while maintaining an acceptable safety profile. The clinical hypothesis for this study is that safety and efficacy of ABBV-105 and ABBV-599 will be maintained over an extended period of treatment.
Objective(s) and Endpoint(s):	The primary objective of this study is to evaluate the long-term safety, tolerability, and efficacy of ABBV-105 and ABBV-599 in RA subjects who have completed Study M16-063. **Efficacy Endpoints** There is no primary endpoint since this is the extension to the feeder Study M16-063. Efficacy endpoints for this study, measured at each study visit, include the following: • Change in disease activity score (DAS)28 (C-reactive protein [CRP]) from baseline of Study M16-063; • Proportion of subjects achieving DAS Low Disease Activity (LDA), defined as DAS28 CRP ≤ 3.2; • Proportion of subjects achieving DAS Clinical Remission (CR), defined as DAS28 CRP < 2.6; • Change in clinical disease activity index (CDAI) from baseline of Study M16-063; • Proportion of subjects achieving LDA based on CDAI criteria, defined as CDAI ≤ 10; • Proportion of subjects achieving CR based on CDAI criteria, defined as CR ≤ 2.8; • Proportion of subjects achieving American College of

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	Rheumatology (ACR) 20/50/70 response; • Change in individual components of ACR from baseline of Study M16-063, to include swollen joint count (SJC), tender joint count (TJC), Patient's Assessment of Pain (using visual analog scale, VAS), Patient Global Assessment of Disease Activity (PtGA), Physician Global Assessment of Disease Activity (PhGA), Health Assessment Questionnaire Disability Index (HAQ-DI), and high-sensitivity C-reactive protein (hsCRP). • Change in Morning Stiffness from baseline of Study M16-063. **Safety Endpoints** Safety evaluations include adverse event (AE) monitoring, physical examinations, vital sign measurements, electrocardiogram (ECG), and clinical laboratory testing (hematology, chemistry, and urinalysis) as a measure of safety and tolerability for the entire study duration.
Investigator(s):	Multi-center
Study Site(s):	The current assumption is to include approximately 39 sites in Canada and the European Union. Depending on operational aspects, the number, allocation, and location of sites may be modified.
Study Population and Number of Subjects to be Enrolled:	This long-term extension (LTE) study will enroll subjects who have completed Study M16-063. Only those subjects who have met all of the specified eligibility criteria will have an option to enter into the LTE study to receive continued therapy, provided the subject is willing and the investigator believes that continuing therapy is appropriate. Based on discontinuation criteria mandating efficacy, it is estimated that 20 - 60% of subjects (i.e., between 40 and 120 subjects) will ultimately complete the LTE.
Investigational Plan:	This is a Phase 2, double-blind, multicenter, LTE study to assess the safety, tolerability, and efficacy of ABBV-105 and ABBV-599 in RA subjects who have completed Study M16-063. Subjects who meet eligibility criteria and enter the study on ABBV-105, ABBV-599, or upadacitinib from Study M16-063 will continue on their previously-assigned treatment through the end of the LTE study. Subjects who meet eligibility criteria and enter the study on placebo for both ABBV-105 and upadacitinib from Study M16-063 will receive ABBV-599. The duration of the LTE study will be approximately 52 weeks. This includes a 48-week double-blind treatment period with study visits conducted at Weeks 18, 24, 30, 36, 48, and 60 from the baseline visit of Study M16-063. In addition, subjects will also have a telephone follow-up call 30 days after their last visit to determine the status of any ongoing AEs/serious adverse events (SAEs) or the occurrence of any new AEs/SAEs.
Key Eligibility Criteria:	Eligible subjects will have completed Study M16-063 (i.e., the preceding study of ABBV-105 and ABBV-599) and will have not developed any laboratory or clinical discontinuation criteria as defined in that study. Subjects must also not be currently enrolled or planning to enroll in any other interventional clinical study and must not require

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	vaccination with any live vaccine during study participation (including at least 30 days after the last dose of study drug). Additional eligibility criteria are listed in the protocol Section 5.1.
Study Drug and Duration of Treatment:	Study drug treatment assignments include the following: • Group 1: ABBV-599 (ABBV-105 60 mg and upadacitinib 15 mg) administered once a day (QD), • Group 2: ABBV-105 60 mg and upadacitinib placebo QD, • Group 3: ABBV-105 20 mg and upadacitinib placebo QD • Group 4: ABBV-105 5 mg and upadacitinib placebo QD, and • Group 5: Upadacitinib 15 mg and ABBV-105 placebo QD. At each visit where study drug is dispensed, each subject will receive 4 bottles of study drug; three of the bottles will contain capsules of ABBV-105 or matching placebo, and the remaining bottle will contain tablets of upadacitinib or matching placebo, all manufactured by AbbVie. Subjects will be instructed to take 1 capsule of ABBV-105 or placebo from each of the 3 dispensed bottles per day and 1 tablet of upadacitinib or placebo from the remaining dispensed bottle per day. Study drug should be taken orally at approximately the same time each day, with or without food.
Date of Protocol Synopsis:	06 February 2020

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2 INTRODUCTION

2.1 Background and Rationale

Why This Study Is Being Conducted

This study will provide data on the long-term safety, tolerability, and efficacy of ABBV-105 and ABBV-599 in rheumatoid arthritis (RA) subjects who have completed the Phase 2 study of these compounds (Study M16-063). ABBV-105 is a novel, covalent Bruton's tyrosine kinase (Btk) inhibitor being developed for the treatment of immune-mediated inflammatory diseases including RA. ABBV-105 may be given alone or in combination with upadacitinib, which is known as ABBV-599.

Btk is a non-receptor tyrosine kinase expressed in multiple immune cell types associated with the pathogenesis of RA and other autoimmune diseases. Btk is required for the propagation of pro-inflammatory signals downstream of immunoreceptors that promote autoimmune disease pathogenesis. Compared to other Btk inhibitors, such as CC-292 (Celgene) and ibrutinib (Pharmacyclics/Janssen), ABBV-105 showed better potency, superior selectivity, and less off-target activity, which is considered favorable for administration in humans.

Upadacitinib is a novel Janus kinase (JAK) inhibitor, which displays unique selectivity for the JAK1 receptor. Upadacitinib is currently being developed for the treatment of adult patients with moderately to severely active RA (Phase 3), psoriatic arthritis (Phase 3), atopic dermatitis (Phase 3), Crohn's disease (Phase 3), ulcerative colitis (Phase 2), axial spondyloarthritis (Phase 2), and giant cell arteritis (Phase 2). Development of other indications of interest (i.e., dermatomyositis and/or Takayasu arteritis) are under discussion. As of 20 June 2017, a total of 1232 subjects have received upadacitinib, which includes 469 healthy volunteers, 553 RA patients, and 210 Crohn's disease patients. Upadacitinib was generally well-tolerated, and the types of adverse events (AEs) seen were typical of patients treated with immunosuppressant therapies.

ABBV-105 given alone or as the ABBV-599 combination therapy (with upadacitinib) are anticipated to be effective in decreasing signs and symptoms associated with active RA in patients with inadequate response or intolerance to biologic disease-modifying antirheumatic drugs (bDMARDs) by interfering with the JAK1/Btk pathways. Concurrent inhibition of JAK1/Btk pathways in RA may increase percent of those responding, as well as depth of response (relative to inhibiting either pathway alone), while maintaining an acceptable safety profile.

Clinical Hypothesis

The safety and efficacy of ABBV-105 and ABBV-599 will be maintained over an extended period of treatment.

2.2 Benefits and Risks to Subjects

Preclinical toxicology studies of ABBV-105 in animals and ex vivo human samples suggest that the potential risks to human subjects of ABBV-105 are anemia, bleeding associated with platelet

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dysfunction, and lymphopenia. Reductions in lymphocytes and the known mechanism of action suggest the potential for an increased susceptibility to infection.

ABBV-105 alone and the ABBV-599 combination therapy (with upadacitinib) were well-tolerated with no serious adverse events (SAEs) observed in healthy adult subjects at various doses in 3 Phase 1 studies (Studies M16-356, M16-357, and M16-044). The current study is a continuation of the Phase 2 study of ABBV-105 and ABBV-599 in RA (Study M16-063). Taken together, the safety data from the Phase 1 program and the safe and successful completion of Study M16-063 support further development of ABBV-105 and ABBV-599 in Phase 2 in subjects with RA.

The data from over 4,000 RA patients treated with upadacitinib support an acceptable safety profile and a positive risk-benefit for treatment of adult patients with moderately to severely active RA.

Data from the primary efficacy analyses of the 5 pivotal Phase 3 clinical studies for the upadacitinib RA development program consistently demonstrated the efficacy of upadacitinib 15 mg QD and 30 mg QD, with both doses of upadacitinib meeting all primary and ranked key secondary endpoints across all studies which included all lines of therapy (methotrexate [MTX]-naïve, conventional synthetic disease-modifying antirheumatic drug [csDMARD]/MTX-inadequate responder [IR], and biologic disease-modifying antirheumatic drug [bDMARD]-IR). Upadacitinib 15 mg QD also demonstrated superiority over adalimumab across a broad range of efficacy measures. Overall, the efficacy data in the RA development program provide substantial evidence to support the use of upadacitinib as monotherapy or in combination with MTX and/or csDMARDs for the treatment of adults with moderately to severely active RA.

Serious infections and herpes zoster are identified risks for upadacitinib therapy. The rates of serious infections and herpes zoster for upadacitinib therapy are within the range of other marketed JAK inhibitor products.

In regarding to the potential for malignancy, per upadacitinib Investigator's Brochure version 18.0:

Few malignancies were reported in the controlled portions of the upadacitinib Phase 2 and 3 clinical studies precluding any conclusions about rates between treatment groups. The interim rate of total malignancies excluding and including non-melanoma skin cancer (NMSC) on upadacitinib in the Phase 2 open label extension Study M13-538, which includes long-term treatment data, are both 0.7 E/100 PY. The malignancy types reported in the clinical program have been consistent with that anticipated in the study population including solid tumors such as breast, prostate and lung cancer, lymphoma, and NMSC. A number of subjects with malignancy had pre-existing risk factors for malignancy and/or prior history of treatment with other immunosuppressive therapy.

The malignancy rate is higher in the upadacitinib 30 mg group compared to the 15 mg treatment group; however, the difference in rates is related to more cases of NMSC and not other malignancy types.

For further details, please see findings from completed studies, including safety data, in the most recent ABBV-105 and upadacitinib Investigator's Brochures.

For safety monitoring, the following are included in the protocol:

- Subjects meeting discontinuation criteria as part of the M16-063 study will be excluded.

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- If a subject develops a serious infection or opportunistic infection with study treatment, study drug should be interrupted, and appropriate treatment of the infection should be initiated.
- SAEs of infection will be reviewed on a real time basis and queried for additional information as clinically indicated.
- A supplemental herpes zoster form will be used to collect additional information for any herpes zoster infections.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The primary objective of this study is to evaluate the long-term safety, tolerability, and efficacy of ABBV-105 and ABBV-599 in RA subjects who have completed Study M16-063.

3.2 Efficacy Endpoints

There is no primary efficacy endpoint since this is the extension to the feeder Study M16-063. Efficacy endpoints for this study, measured at each study visit, include the following:

- Change in disease activity score (DAS)28 (C-reactive protein [CRP]) from baseline of Study M16-063;
- Proportion of subjects achieving DAS Low Disease Activity (LDA), defined as DAS28 CRP ≤3.2;
- Proportion of subjects achieving DAS Clinical Remission (CR), defined as DAS28 CRP < 2.6;
- Change in clinical disease activity index (CDAI) from baseline of Study M16-063;
- Proportion of subjects achieving LDA based on CDAI criteria, defined as CDAI ≤ 10;
- Proportion of subjects achieving CR based on CDAI criteria, defined as CDAI ≤ 2.8;
- Proportion of subjects achieving American College of Rheumatology (ACR) 20/50/70 response. A subject will be considered an ACR 20/50/70 responder if:
  - The swollen joint count (SJC) and tender joint count (TJC) have decreased from baseline of Study M16-063 by 20/50/70% or more.
  - At least 3 of the 5 remaining ACR core set measures (i.e., Patient's Assessment of Pain [using visual analog scale, VAS], Patient Global Assessment of Disease Activity [PtGA], Physician Global Assessment of Disease Activity [PhGA], Health Assessment Questionnaire Disability Index [HAQ-DI], and high-sensitivity C-reactive protein [hsCRP]) show reduction of 20/50/70% or more from baseline of Study M16-063.
- Change in individual components of ACR from baseline of Study M16-063, to include:
  - SJC,
  - TJC,

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- Patient's Assessment of Pain (using VAS),
- PtGA,
- PhGA,
- HAQ-DI, and
- hsCRP.

- Change in Morning Stiffness from baseline of Study M16-063.

3.3 Safety Endpoints

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, electrocardiogram (ECG), and clinical laboratory testing (hematology, chemistry, and urinalysis) as a measure of safety and tolerability for the entire study duration.

An internal data monitoring committee (DMC) will review unblinded safety data on a cohort level throughout the course of the study. A separate DMC charter has been prepared outside of the protocol and describes the roles and responsibilities of the DMC members, frequency of data reviews, relevant safety data to be assessed, and expectations for blinded communications.

The DMC will be responsible for safeguarding the interests of trial subjects by assessing the safety and, if appropriate, the efficacy data of the interventions during the trial, as well as for monitoring the quality and integrity of the clinical trial. The DMC will provide recommendations to the AbbVie contact about stopping, modifying or continuing the trial without modification. The DMC may also formulate recommendations relating to the selection/recruitment/retention of subjects, their management, improving adherence to protocol-specified regimens and retention of subjects, and the procedures for data management and quality control.

The DMC is a multidisciplinary group consisting of clinicians and biostatisticians who, collectively, has knowledge in the management of patients with rheumatoid arthritis (RA) and experience in the conduct and monitoring of randomized clinical trials. The DMC reviews the available safety data, and as applicable, the critical efficacy endpoints, assessing risks and benefits, and recommends to the AbbVie Contact whether to continue without change, modify, or stop the Study M16-063 clinical trial.

All DMC members will be internal AbbVie members with expertise in clinical safety monitoring and who have no affiliation with ABBV-599. Following initiation of the study, DMC members will have no involvement in the conduct of Study M16-063 or other ABBV-599 clinical trials outside their role on the DMC. All DMC members have agreed to not discuss unblinded data with those who have involvement with Study M16-063 or ABBV-599 development until the Study M16-063 unblinded information is made available to the team.

An independent Cardiovascular Adjudication Committee (CAC) will adjudicate blinded cardiac and cerebrovascular events. A CAC charter has been prepared separately from the protocol and defines objective, scope, frequency, and triggers of data reviews.

The clinical trial is to be discontinued or terminated in case of an unacceptable risk, relevant toxicity, or a negative change in the risk/benefit assessment. This might include the occurrence of adverse events

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of which character, severity or frequency is new in comparison to the existing risk profile. In addition any data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment might cause discontinuation or termination of the study.

3.4 Biomarker Research

Optional samples (whole blood, serum, and plasma) will be collected at specific time points as described in the Activity Schedule (Appendix D) to evaluate known and or novel disease related or drug related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites. The objective of research is to analyze samples for biomarkers that will help to understand RA, related conditions, and response to treatment with ABBV-105 and upadacitinib or similar compounds. Research on samples collected in Germany will be limited to RA, ABBV-105, and upadacitinib. Research may also include changes in epigenetics, gene expression, and proteomics that may be associated with RA, related conditions, or the subject's response to treatment. This research is exploratory in nature, and the results may not be included with the clinical study report.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 2, double-blind, multicenter, long-term extension (LTE) study to assess the safety, tolerability, and efficacy of ABBV-105 and ABBV-599 in RA subjects who have completed Study M16-063. Subjects who meet eligibility criteria (Section 5.1) and enter the study on ABBV-105, ABBV-599, or upadacitinib from Study M16-063 will continue on their previously-assigned treatment through the end of the LTE study. Subjects who meet eligibility criteria and enter the study on placebo for both ABBV-105 and upadacitinib from Study M16-063 will receive ABBV-599. Study drug treatment assignments include the following:

- Group 1: ABBV-599 (ABBV-105 60 mg and upadacitinib 15 mg) administered once a day (QD),
- Group 2: ABBV-105 60 mg and upadacitinib placebo QD,
- Group 3: ABBV-105 20 mg and upadacitinib placebo QD
- Group 4: ABBV-105 5 mg and upadacitinib placebo QD, and
- Group 5: Upadacitinib 15 mg and ABBV-105 placebo QD.

This study plans to enroll subjects who completed Study M16-063 at approximately 39 sites in Canada and the European Union. The number, allocation, and location of sites may vary depending on operational aspects of the study. Study sites and subjects will remain blinded for the duration of the study.

The duration of the LTE study will be approximately 52 weeks. This includes a 48-week double-blind treatment period with study visits conducted at Weeks 18, 24, 30, 36, 48, and 60 from the baseline visit of Study M16-063. In addition, subjects will also have a telephone follow-up call 30 days after their last visit to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

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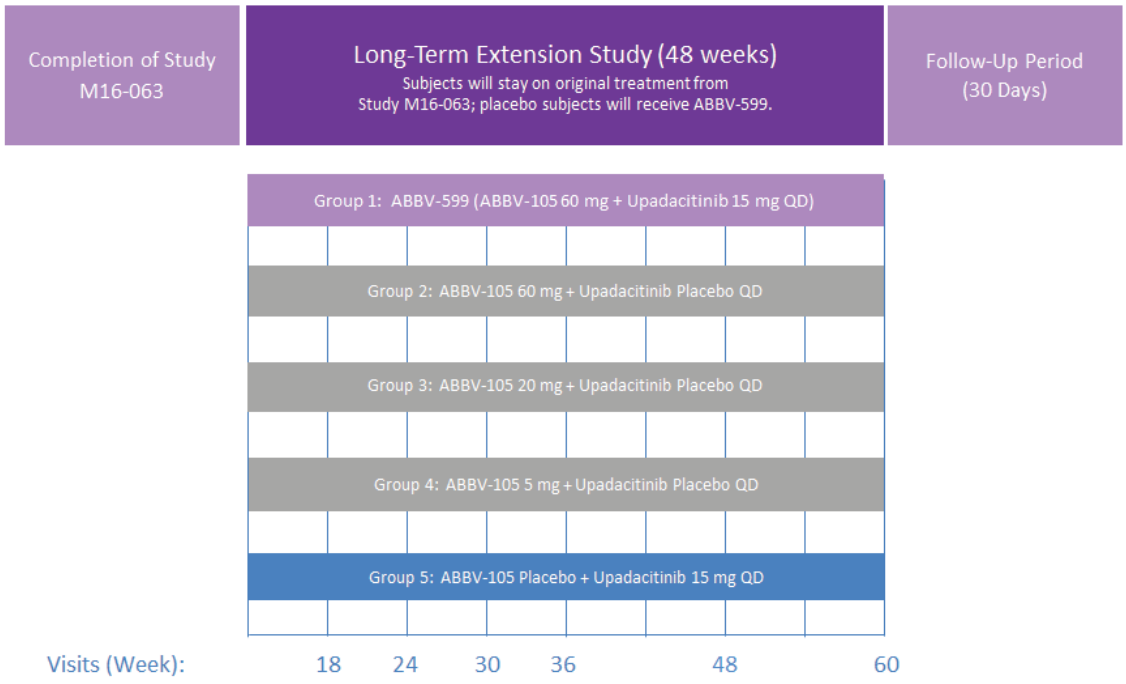
The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual.

Figure 1. Period 1 Schematic



QD = administered once a day

4.2 Discussion of Study Design

Choice of Control Group

Subjects will roll over from Study M16-063 and continue on their originally randomized treatment, with the exception of those originally randomized to placebo, who will roll over to ABBV-599. The objective of this LTE study is to evaluate long term safety and efficacy of ABBV-105 and ABBV-599, and thus primary comparison will be relative to the safety and efficacy profile observed in each arm during the initial randomized study.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with RA. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

This LTE study will enroll subjects who have completed Study M16-063. Only those subjects who have met all of the specified eligibility criteria will have an option to enter into the LTE study to receive

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continued therapy, provided the subject is willing and the investigator believes that continuing therapy is appropriate.

Selection of Doses in the Study

Since the study is a continuation of the initial Phase 2 dose exploration study of ABBV-105 and ABBV-599, the doses selected for this study are the same as those used previously in Study M16-063. These doses were determined based on an analysis of pharmacokinetic, pharmacodynamic, and safety data from Phase 1 studies in healthy volunteers for ABBV-105 and Phase 2 and Phase 3 studies for upadacitinib, in addition to efficacy data for upadacitinib in RA.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects or their legally authorized representative must voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Subjects have completed Study M16-063 (i.e., the preceding study of ABBV-105 and ABBV-599) and have not developed any laboratory or clinical discontinuation criteria as defined in that study.

  Relevant Study M16-063 eligibility requirements applicable to Study M16-763 are as follows:

  a. Subjects or their legally authorized representative must voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

  b. Adult **male or female**, at least 18 years old.

  c. **Laboratory values** not meeting toxicity management criteria from the Study M16-063 study:

  d. Diagnosis of RA for ≥ 3 months based on the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA.

  e. No history of any of the following cardiovascular conditions:

  - Moderate to severe congestive heart failure (New York Heart Association Class III or IV).
  - Recent history (within past 6 months) of cerebrovascular accident (CVA), myocardial infarction, and/or coronary stenting.
  - Uncontrolled hypertension as defined by a persistent systolic blood pressure (BP) > 160 mmHg or diastolic BP > 100 mmHg. For subjects with known hypertension, the

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subject's BP must be stable for at least 4 weeks on current, stable anti-hypertensive medications.

- Prior unprovoked deep vein thrombosis or pulmonary embolism (PE) (i.e., any spontaneous event not directly attributable to trauma or vascular instrumentation).
- Any other condition which, in the opinion of the Investigator, would put the subject at risk by participating in the protocol.

f. No history of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA (including but not limited to gout, systemic lupus erythematosus, psoriatic arthritis, axial spondyloarthritis including ankylosing spondylitis and non-radiographic axial spondyloarthritis, reactive arthritis, overlap connective tissue diseases, scleroderma, polymyositis, dermatomyositis, fibromyalgia [currently with active symptoms], or any arthritis with onset prior to age 17 years). Current diagnosis of secondary Sjogren's Syndrome is permitted.

g. Must not have been treated with any investigational drug, other than those supplied in Study M16-063, within 30 days or five half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study, other than Study M16-063.

h. Females must not be pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.

i. For all females of child-bearing potential: a **negative serum pregnancy test** at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug in the Study M16-063 study as well as persistently negative urine pregnancy test throughout Study M16-063 and at entrance into this study.

j. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control** that is effective from Study Day 1 through at least 30 days after last dose of study drug. Female subjects of non-childbearing potential do not need to use birth control.

k. Must not have any active or recurrent viral infection that, based on the Investigator's clinical assessment, makes the subject an unsuitable candidate for the study, including hepatitis B virus (HBV) or hepatitis C virus (HCV), recurrent or disseminated (even a single episode) herpes zoster, disseminated (even a single episode) herpes simplex, or human immunodeficiency virus (HIV).

   Active HBV, HCV, and HIV are defined as:

   HBV: Hepatitis B surface antigen (HBs Ag) positive (+) or, for hepatitis B core antibody (HBc Ab) positive subjects, detection of HBV DNA by polymerase chain reaction (PCR);

   HCV: HCV RNA detectable in any subject with anti-HCV antibody (HCV Ab);

   HIV: Confirmed positive anti-HIV antibody (HIV Ab) test.

l. Must not have active TB or meets TB exclusionary parameters (defined as the presence of active TB or latent TB not adequately treated as per protocol requirements).

m. Must not have used known strong cytochrome P450 (CYP)3A or CYP1A2 inhibitors or strong CYP3A or CYP1A2 inducers from Screening through the end of the study.

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n. Must not have had receipt of any live vaccine within 4 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 4 weeks after the last dose of oral study drug.

o. Must not have a history of any malignancy except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix.

p. Must not have a history of clinically significant (per Investigator's judgment) drug or alcohol abuse within the last 6 months.

q. Must not have a history of gastrointestinal perforation (other than appendicitis or penetrating injury), diverticulitis or significantly increased risk for gastrointestinal perforation per investigator judgment.

r. Must not have any conditions that could interfere with drug absorption including but not limited to short bowel syndrome.

s. Must not be a recipient of an organ transplant.

t. Must not have history of clinically significant medical conditions or any other reason that in the opinion of the Investigator would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug.

u. Must not have had an active infection(s) requiring treatment with parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the first dose of study drug.

v. Must not have a history of an allergic reaction or significant sensitivity to constituents of the study drugs (and its excipients) and/or other products in the same class.

w. Subjects must have been treated for ≥ 3 months with ≥ 1 bDMARD therapy but continue to exhibit active RA or had to discontinue due to intolerability or toxicity, irrespective of treatment duration.

x. Subjects must have been receiving csDMARD therapy ≥ 3 months prior to Study M16-063 baseline visit.

   The following csDMARDs are allowed: oral or parenteral methotrexate (MTX) (7.5 to 25 mg/week), sulfasalazine (≤ 3000 mg/day), hydroxychloroquine (≤ 400 mg/day), chloroquine (≤ 250 mg/day), and leflunomide (≤ 20 mg/day).

   A combination of up to two background csDMARDs is allowed EXCEPT the combination of MTX and leflunomide.

y. Subjects must have discontinued all bDMARDs prior to the first dose of study drug. The washout period for bDMARDs prior to the first dose of study drug is specified below or should be at least five times the mean terminal elimination half-life of a drug:

   ≥ 4 weeks for etanercept;

   ≥ 10 weeks for adalimumab, infliximab, certolizumab, golimumab, tocilizumab, and abatacept;

   ≥ 1 year for rituximab OR ≥ 6 months if B cells have returned to pretreatment level or normal reference range (central lab) if pretreatment levels are not available.

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z. Subjects must have discontinued all high-potency opiates at least 1 week and oral traditional Chinese medicine for at least 4 weeks prior to the first dose of study drug (refer to Section 5.3 for prohibited medications).

- 3. Subject is willing and/or able to comply with procedures required in this protocol.

Concomitant Medications

- 4. Subject must not be currently enrolled in any study (except the preceding Study M16-063) or planning to enroll in another interventional clinical study while participating in this study.
- 5. Subject must not require vaccination with any live vaccine during study participation, including at least 30 days after the last dose of study drug.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
  - Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 40 IU/L.
  - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

- Females, of Childbearing Potential

  Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 30 days after the last dose of study drug. Females must commit to one of the following methods of birth control:

  - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline Day 1.
  - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline Day 1.
  - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
  - Intrauterine device (IUD).
  - Intrauterine hormone-releasing system (IUS).

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- To have a vasectomized partner(s) (the vasectomized partner[s] has received medical assessment of the surgical success and is the sole sexual partner of the trial subject).
- To practice true abstinence (if acceptable per local guidelines), defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If required per local practices, male or female condom with or without spermicide OR cap, diaphragm, or sponge with spermicide should be used in addition to one of the highly effective birth control methods listed above (excluding true abstinence). A condom is required in the following countries: UK, Germany, and Spain.

Concomitant conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (i.e., MTX, sulfasalazine, etc.) have been prescribed per standard of care prior to study entry and are allowed to be continued during the study. Contraception should continue while the subject is on the concomitant csDMARD(s) and that duration of contraception after discontinuation of the csDMARD(s) should be based on the local label. Additional local requirements may apply.

5.3 Prohibited Medications and Therapy

JAK Inhibitor

Initiation of any new JAK inhibitors (including, but not limited to, tofacitinib [Xeljanz®], baricitinib [Olumiant®], and filgotinib) is not allowed.

Corticosteroids

Oral corticosteroids > 10 mg prednisone/day or equivalent and intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, and intra-tendon sheath corticosteroids are NOT allowed during this study except as described in Section 5.4 (Prior and Concomitant Therapy) for treatment of an RA flare, as defined by the investigator.

Any csDMARD/Immunosuppressive Therapy Not Listed in Section 5.4 (Prior and Concomitant Therapy)

All biologic therapies are prohibited during the study. Examples of biologic therapies include but are not limited to the following:

- Humira® (adalimumab)
- Enbrel® (etanercept)
- Remicade® (infliximab)
- Kineret® (anakinra)
- Rituxan® (rituximab)
- Cimzia® (certolizumab pegol)
- Simponi® (golimumab)

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- Actemra® (tocilizumab)
- Raptiva® (efalizumab)
- Tysabri® (natalizumab)
- Stelara® (ustekinumab)
- Benlysta® (belimumab)
- Orencia (abatacept)

Strong CYP3A or CYP1A2 Inhibitors or Inducers

Systemic use of known strong inhibitors or inducers of CYP3A or CYP1A2 is excluded from the Screening Visit through the end of the study. The most common strong CYP3A or CYP1A2 inhibitors and inducers are listed in Table 1.

Table 1. Examples of Commonly Used Strong CYP3A or CYP1A2 Inhibitors and Inducers

Strong CYP3A Inhibitors	**Strong CYP3A Inducers**
Boceprevir Cobicistat Clarithromycin Conivaptan Grapefruit (fruit or juice) Indinavir Itraconazole Ketoconazole Lopinavir/Ritonavir Mibefradil Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telaprevir Telithromycin Troleandomycin Voriconazole	Carbamazepine Phenytoin Rifampin Rifapentine St. John's Wort
Strong CYP1A2 Inhibitors	**Strong CYP1A2 Inducers**
Fluvoxamine Ciprofloxacin Enoxacin Zafirlukast	Rifampin

Live Vaccines

Use of live vaccines is prohibited during the study and must be avoided for four weeks after the last dose of study drug. Examples of live vaccines include, but are not limited to, the following:

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- Monovalent live influenza A (H1N1) (intranasal);
- Seasonal trivalent live influenza (intranasal);
- Herpes zoster;
- Rotavirus;
- Varicella (chicken pox);
- Measles-mumps-rubella or measles mumps rubella varicella;
- Oral polio vaccine;
- Smallpox;
- Yellow fever;
- Bacille Calmette-Guérin (BCG);
- Typhoid.

5.4 Prior and Concomitant Therapy

Subjects should continue on their previous background csDMARD therapy from Study M16-063, restricted to the following: oral or parenteral methotrexate (7.5 to 25 mg/week), sulfasalazine (≤ 3000 mg/day), hydroxychloroquine (≤ 400 mg/day), chloroquine (≤ 250 mg/day), and/or leflunomide (≤ 20 mg/day). Combinations of up to two csDMARDs are allowed except for the combination of MTX and leflunomide.

At any time, the csDMARD dose may be decreased for safety reasons. Subjects taking MTX should take a dietary supplement of oral folic acid (or equivalent, such as folinic acid) throughout study participation. Folic acid dosing and timing of regimen should be followed according to Investigator's instructions. AbbVie will not provide the csDMARDs (or folic acid, if taking MTX).

Subjects should continue on their stable doses of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen/paracetamol, oral corticosteroids (equivalent to prednisone ≤ 10 mg/day), or inhaled corticosteroids.

- If taking any of the above on a scheduled basis, subjects should continue to take them as they did at study entry with no change in dose or frequency, including on study visit days.
- If subject was not taking any of the above at baseline, these must not be initiated except where permitted by protocol (i.e., after Week 18).
- If taking any of the above, including low-potency analgesics (i.e., tramadol, codeine, hydrocodone, or propoxyphene) at baseline on an as-needed (PRN) basis, subjects should continue to use them for the same reason and same dose each time, but they should not be taken within the 24 hours prior to any study visit to avoid bias in outcome measurements.

Calculation of the Clinical Disease Activity Index (CDAI) is required to determine if a subject fails to achieve LDA. Calculation of CDAI will be performed at the Week 18 visit by Interactive Response

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Technology (IRT) with input from site personnel on joint counts and PtGA and PhGA score. The calculation used to determine CDAI score at Week 18 is as follows:

$$CDAI = TJC28 + SJC28 + PtGA\ (cm) + PhGA\ (cm)$$

Beginning at Week 18, subjects who fail to achieve CDAI ≤ 10 should have background medication(s) adjusted or initiated. Initiation of or change in corticosteroids, NSAIDs, or acetaminophen, or adding/increasing csDMARD doses (restricted to oral or parenteral MTX, sulfasalazine, hydroxychloroquine, chloroquine, and leflunomide, except for the combination of MTX and leflunomide), is allowed as per local label and at investigator discretion. If necessary, a burst of systemic corticosteroids (maximum dose of 0.5 mg/kg of prednisone or its equivalent) is allowed, after which subject should resume their usual daily oral corticosteroid dose.

Intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, and intra-tendon sheath injections of corticosteroids, at dosage and frequency per standard of care, are allowed after the Week 18 assessments have been performed and at time points thereafter. For the analysis of the TJC and SJC, injected joints will be considered "not assessable" for 3 months from the time of the intra-articular injection.

In the event of tolerability (or other safety) issues, the doses of these medications may be decreased or discontinued with substitution of another permitted medication from that class. PRN use of inhaled corticosteroids is permitted at any time.

Study drug interruption is allowed up to 30 consecutive days. If the subject undergoes elective surgery, the study drug should be interrupted 2 weeks prior to the planned surgery. If the subject must undergo emergency surgery, the study drug should be interrupted at the time of surgery. In either case, study drug may be reintroduced once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject receives during the study should be recorded through the follow-up phone call 30 days after the last treatment visit (Week 60).

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with ABBV-105 or ABBV-599 can be located in the ABBV-105 or upadacitinib Investigator's Brochures.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie Therapeutic Area Medical Director.
- Serious infections (e.g., sepsis) that cannot be adequately controlled within 2 weeks by anti-infective treatment or would put the subject at risk for continued participation in the trial as determined by the Investigator.

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- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- Subject is non-compliant with tuberculosis (TB) prophylaxis (if applicable) or develops active TB at any time during the study.
- The subject becomes pregnant while on study drug.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.
- Subject develops a gastrointestinal perforation.

In addition, the following discontinuation criteria also apply:

- Subjects not responding to therapy can discontinue study drug (or withdraw from study) at any time for any reason during the study in order to receive standard of care.
- Subjects who demonstrate worsening of joint count (SJC and/or TJC) at 2 consecutive visits (scheduled or unscheduled) should be discontinued from study drug and treated with standard of care at the discretion of the clinician.
- Starting at the Week 18 visit (after the Week 18 assessments have been performed) and at visits thereafter, subjects who fail to achieve at least 20% improvement in TJC and SJC should be discontinued.
- Starting at the Week 18 visit (after the Week 18 assessments have been performed) and at visits thereafter, subjects who fail to achieve CDAI ≤ 10 should have background medication(s) adjusted or initiated (i.e., initiation of or change in corticosteroids, NSAIDs, acetaminophen or adding or increasing doses in csDMARDs [restricted to oral or parenteral MTX, sulfasalazine, hydroxychloroquine, chloroquine and leflunomide except the combination of MTX and leflunomide is allowed as per local label]).
- Starting at the Week 18 visit (after Week 18 assessments have been performed) and at visits thereafter, intra-articular, intramuscular, intravenous, trigger point or tender point, intra-bursa, and intra-tendon sheath injections of corticosteroids, dosage and frequency per standard of care are allowed. For the analysis of the TJC and SJC, injected joints will be considered "not assessable" for 3 months from the time of the intra-articular injection.
- Starting at the Week 24 visit and at visits thereafter, subjects achieving 20% improvement in TJC and SJC but not achieving CDAI ≤10 should be considered for discontinuation to standard of care at the discretion of the clinician.

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Subjects who prematurely discontinue study drug should complete a Premature Discontinuation (PD) Visit as soon as possible, preferably within 2 weeks of discontinuation. See Section 5.6 for information regarding early discontinuation.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

5.6 Follow-Up for Subject Withdrawal from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

Following discontinuation of study drug, the subject should be treated in accordance with the investigator's best clinical judgment irrespective of whether the subject decides to continue participation in the study. In addition, all future rescue- and efficacy-driven discontinuation criteria no longer apply. This includes 20% TJC/SJC calculations at Weeks 12 through 24, Weeks 36 through 40 and Week 48 and thereafter, as well as CDAI calculation at Week 26, if applicable. If at any point a subject no longer wants to provide assessments (withdrawal of informed consent) following discontinuation of study drug, a second PD visit is not required.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the PD visit should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved.

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate electronic case report form (eCRF) page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject should be treated in accordance with the Investigator's best clinical judgment irrespective of whether the subject decides to continue participation in the study.

If a subject withdraws from the main study, biomarker research samples will continue to be stored and analyzed. A subject must contact the study investigator if they no longer want their samples to be stored and analyzed. Once AbbVie is notified, no new information will be collected, no new analysis will be started, and the samples will be destroyed unless a regulatory authority requires AbbVie to keep them. However, if AbbVie (or people or companies working with AbbVie) collected any information or

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did any testing before withdrawal, AbbVie (or people or companies working with AbbVie) will still use and disclose such information, use the test results, and keep the data generated from the samples.

5.7 Study Drug

Information about the study drug and placebo used in this study is presented in Table 2.

Table 2. Study Drug

	Investigational Product	Investigational Product	Investigational Product Placebo	Investigational Product Placebo
Investigational Product Name	ABBV-105	Upadacitinib	ABBV-105 Placebo	Upadacitinib Placebo
Active Ingredient	ABBV-105	Upadacitinib	N/A	N/A
Mode/Route of Administration	Oral	Oral	Oral	Oral
Combination Drugs	N/A	N/A	N/A	N/A
Formulation				
Dosage Form	Capsule	Film-Coated Tablet	Capsule	Film-Coated Tablet
Dose and Units	5 mg, 20 mg	15 mg	N/A	N/A
Drug Preparation	N/A	N/A	N/A	N/A
Masking	N/A	N/A	N/A	N/A
Frequency of Administration	Daily	Daily	Daily	Daily
Storage Conditions	Room Temperature (15° to 25°C/ 59° to 77°F)	Room Temperature (15° to 25°C/ 59° to 77°F)	Room Temperature (15° to 25°C/ 59° to 77°F)	Room Temperature (15° to 25°C/ 59° to 77°F)

N/A = not applicable

At each visit where study drug is dispensed, each subject will receive 4 bottles of study drug; three of the bottles will contain capsules of ABBV-105 or matching placebo, and the remaining bottle will contain tablets of upadacitinib or matching placebo, all manufactured by AbbVie. Subjects will be instructed to take 1 capsule of ABBV-105 or placebo from each of the 3 dispensed bottles per day and 1 tablet of upadacitinib or placebo from the remaining dispensed bottle per day. Study drug should be taken orally at approximately the same time each day, with or without food. If subjects should forget to take any of their study drug at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember, as long as it is at least 10 hours before their next scheduled dose. Otherwise, they should take the next dose at the next scheduled dosing time.

Subject dosing will be recorded on a subject dosing diary. The subject will be instructed to return all drug containers, even if empty, to the study site personnel at each study visit. Study site personnel will document compliance.

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AbbVie will not supply drug other than ABBV-105, upadacitinib, and matching placebo for this study. ABBV-105, upadacitinib, and matching placebo will be packaged in bottles with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements, and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location.

Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

5.8 Randomization/Drug Assignment

All subjects were assigned a unique identification number by the IRT at the screening visit for Study M16-063. Subjects who enter the study on active ABBV-105 and/or upadacitinib from Study M16-063 will continue on their previously-assigned treatment through the end of the LTE study. Subjects who previously received placebo treatment during Study M16-063 will receive ABBV-599 in the LTE study.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study. To maintain the blind, the ABBV-105 capsules and matching placebo capsules and upadacitinib tablets and matching placebo tablets provided for the study will be identical in appearance.

In the event of a medical situation that requires unblinding of the study drug assignment, the Investigator is requested to contact the AbbVie Therapeutic Area Medical Director prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie Therapeutic Area Medical Director, the Investigator can directly access the IRT system via the Unblind Subject transaction, which is available to the Investigator. If the IRT system is unavailable, unblinding may occur by contacting EndPoint technical support via either phone (preferred) or email (support@endpointclinical.com). For country-specific phone numbers, please see the following website: http://www.endpointclinical.com/help-desk/. In the event that the blind is broken before notification to the AbbVie Therapeutic Area Medical Director, we request that the AbbVie Therapeutic Area Medical Director be notified within 24 hours of the blind being broken.

5.9 Protocol Deviations

The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying the IEC/IRB, regulatory authorities (as applicable), and AbbVie.

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6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaints

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 1 business day of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If any of the following AEs in Table 3 are reported, the following supplemental report(s) must be completed.

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Table 3. Adverse Events Requiring Supplemental Reports

Adverse Event	Supplemental Report
Cardiac events **Myocardial infarction or unstable angina** **Heart failure** **Cerebral vascular accident and transient ischemic attack** **Cardiovascular procedures (SAE Supplemental Procedure eCRF)**	MACE eCRF
Discontinuation or interruption of study drug due to a hepatic-related AE **A hepatic-related SAE** **ALT/AST > 8 × ULN or ALT/AST > 3 × ULN with a total bilirubin > 2 × ULN**	Hepatic AE eCRF
Renal impairment **Renal dysfunction** **Renal failure** **Serum creatinine > 2.0 mg/dL**	Renal eCRF
Herpes zoster infection	Herpes Zoster eCRF
Thrombotic events **Non-cardiac, non-CNS embolic or thrombotic event (i.e., deep vein thrombosis or pulmonary embolism)**	Embolic and Thrombotic (non-cardiac, non-CNS) eCRF

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; eCRF = electronic case report form; MACE = major adverse cardiovascular event; SAE = serious adverse event; ULN = upper limit of normal

If an AE meets any of the following criteria, it is to be reported to AbbVie or Contract Research Organization (as appropriate) as a SAE within 24 hours of the site being made aware of the SAE:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.

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Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local requirements.

AEs will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following adverse events of special interest (AESI) will be monitored during the study:

- Serious infections
- Opportunistic infections
- Herpes zoster
- Tuberculosis
- Malignancy (all types)
- Gastrointestinal perforations
- Adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE])
- Anemia
- Neutropenia

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- Lymphopenia
- Increased serum creatinine and renal dysfunction
- Hepatic events and increased hepatic transaminases
- Elevated creatine phosphokinase
- Embolic and thrombotic events (non-cardiac, non-CNS)

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the Rheumatology Common Toxicity Criteria v.2.0. **If no grading criteria are provided for the reported event, then the event should be graded as follows:**

- Mild (Grade 1): Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate (Grade 2): Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).
- Severe (Grade 3): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden);
- Life-threatening (Grade 4): Urgent intervention indicated or death related to AE.

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

No Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 1 working day after the site becomes aware of the pregnancy. Subjects who become pregnant must be discontinued (Section 5.5). Information regarding the pregnancy and the outcome will be collected.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

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6.2 Toxicity Management

The management of specific AEs and laboratory parameters is described in the Operations Manual.

The toxicity management of AEs, including AESIs, consists of safety monitoring (review of AEs on an ongoing basis and periodic/ad hoc review of safety issues by a data monitoring committee [DMC]), interruption of study drug dosing with appropriate clinical management (if applicable), and discontinuation of the subjects from study drug. The management of specific AEs and laboratory parameters is described below.

For subjects who have had study drug discontinued and are instead on standard of care therapies, these toxicity management requirements do not apply (including alerts from the central lab), and any intolerability to standard of care therapies should be managed by the prescribing physician.

Serious Infections: Subjects should be closely monitored for the development of signs and symptoms of infection during and after treatment with study drug. Study drug should be interrupted if a subject develops a serious infection or an opportunistic infection. A subject who develops a new infection during treatment with study drug should undergo prompt diagnostic testing appropriate for an immunocompromised subject. As appropriate, antimicrobial therapy should be initiated, and the subject should be closely monitored. Study drug may be restarted once the infection has been successfully treated. Subjects who develop active TB or experience hepatitis B reactivation must be discontinued from study drug. To further monitor subjects for serious infections, subjects will complete at-home weekly temperature monitoring. If above 100.5 degrees Fahrenheit (38 degrees Celsius), subject should inform their study doctor to assess the need for further evaluation.

Subjects should be advised to follow local public health guidelines in order to prevent subjects enrolled in these trials from acquiring TB.

Serious Gastrointestinal Events: Subjects presenting with the onset of signs or symptoms of a serious gastrointestinal event should be evaluated promptly for early identification of gastrointestinal perforation. If the diagnosis of gastrointestinal perforation is confirmed, the subject must be discontinued from study drug.

Cardiovascular Events (MACE): Subjects presenting with potential cardiovascular events should be carefully monitored. These events will be reviewed and adjudicated by the independent CAC in a blinded manner.

Malignancy: Subjects who develop malignancy other than NMSC or carcinoma in situ of the cervix must be discontinued from study drug. Information, including histopathological results, should be queried for the confirmation of the diagnosis.

ECG Abnormality: Subjects must be discontinued from study drug for an ECG change considered clinically significant and with reasonable possibility of relationship to study drug OR a confirmed absolute QT interval corrected for heart rate using Fridericia's correction formula (QTcF) value > 500 msec.

Management of Select Laboratory Abnormalities: For any given laboratory abnormality, the Investigator should assess the subject and apply the standard of care for medical evaluation and

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treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in the operations manual and may require an appropriate supplemental eCRF be completed. All abnormal laboratory tests that are considered clinically significant by the Investigator will be followed to a satisfactory resolution. If a repeat test is required, the repeat testing must occur as soon as possible.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all subjects who completed Study M16-063 and received at least 1 dose of assigned study drug in Study M16-763. The FAS will be used for efficacy and baseline analyses. Subjects will be grouped according to treatments as randomized for Study M16-063.

The Safety Analysis Set also includes all subjects who completed Study M16-063 and received at least one dose of assigned study drug in Study M16-763. Subjects will be grouped according to treatments actually received in Study M16-763. The Safety Analysis Set will be used for safety analyses.

7.3 Statistical Analyses for Efficacy

Analysis of efficacy endpoints will be conducted on the FAS based on treatments as randomized for Study M16-063. The analysis will be based on As Observed data, and no imputation will be conducted. The analysis treatment groups will be described as follows indicating from Study M16-063 to extension Study M16-763:

- Group 1: ABBV-599 to ABBV-599
- Group 2: ABBV-105 60 to 105 60 mg
- Group 3: ABBV-105 20 to 105 20 mg
- Group 4: ABBV-105 5 to 105 5 mg
- Group 5: Upadacitinib 15 to Upadacitinib 15 mg, and
- Group 6: Placebo to ABBV-599
- Group 7: All ABBV-599 (Group 1 and 6)

The baseline for all efficacy analyses in this study will be the baseline in Study M16-063.

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There is no primary efficacy endpoint and no formal statistical tests will be applied. Only descriptive statistics will be used for all efficacy endpoints. Descriptive statistics will be provided for each treatment group for all visits. These include the number of observations, mean with 95% confidence interval, standard deviation, median, minimum and maximum for continuous endpoints (or the change from baseline measurements), and frequencies and percentages with 95% confidence interval for binary endpoints.

No missing data imputation will be applied. All efficacy analyses will be based on As Observed analysis, and thus a subject who does not have an evaluation at the primary analysis time point will not be included.

Details on efficacy analyses are provided in the SAP.

Sample Size Estimation

This is the LTE study for Study M16-063. All eligible subjects who completed Study M16-063 will be enrolled in this study if the subject signs and dates the informed consent. Based on discontinuation criteria mandating efficacy, it is estimated that 20 - 60% of subjects (i.e., between 40 and 120 subjects) will ultimately complete the LTE.

7.4 Statistical Analyses for Safety

All safety analyses will be performed in the Safety Analysis Set.

All treatment-emergent adverse events (TEAEs), SAEs, AEs leading to discontinuation, and AESI will be collected during the study. A TEAE is defined as an event with onset or worsening after the first study dose of study drug and within 30 days after the last dose of study drug administration. The number and percentages of subjects experiencing TEAEs will be tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class and preferred term. Summaries (including percentages and event per 100 patient-year) of SAEs, deaths, AEs leading to discontinuation, and AESI will be provided as well. For selected laboratory and vital signs parameters, mean change from baseline and percentage of subject with evaluations meeting pre-defined criteria for Potentially Clinically Important values will be summarized.

7.5 Interim Analysis

An unblinded interim analysis to review long-term safety and efficacy will be conducted after the Study M16-063 unblinded Week 12 database lock and analysis. The descriptive statistics will be presented for key efficacy and safety endpoints with all available data at the interim analysis. Detailed interim analyses are provided in the SAP.

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8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

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11 COMPLETION OF THE STUDY

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study and will forward a copy of this report to AbbVie or their representative.

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug, and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Medicines Agency Guidance on Investigator's Signature for Study Reports.

The end of study is defined as the date of the last subject's last contact, which will be a follow-up phone call 30 days after the last dose.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

ACR	American College of Rheumatology
AE	adverse event
ADL	activities of daily living
AESI	adverse event(s) of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	Bacille Calmette-Guérin
bDMARD	biologic disease-modifying antirheumatic drug
Btk	Bruton's tyrosine kinase
CAC	Cardiovascular Adjudication Committee
CDAI	Clinical Disease Activity Index
CNS	central nervous system
CR	clinical remission
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CYP1A2	cytochrome P450 1A2 isoform
CYP3A	cytochrome P450 3A isoform
DAS	disease activity score
DAS28	disease activity score (28 joints)
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EudraCT	European Clinical Trials Database
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire Disability Index
HBV, HCV	hepatitis B virus, hepatitis C virus
HIV	human immunodeficiency virus
hsCRP	high-sensitivity C-reactive protein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

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IEC	independent ethics committee
IGRA	interferon gamma release assay
IMP	Investigational Medicinal Product
IRB	institutional review board
IRT	interactive response technology
IU	International Unit
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
JAK	Janus kinase
LDA	low disease activity
LTE	long-term extension
MACE	major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NMSC	non-melanoma skin cancer
NSAID	nonsteroidal anti-inflammatory drug
PD	premature discontinuation
PhGA	Physician's Global Assessment of Disease Activity
PtGA	Patient's Global Assessment of Disease Activity
PRN	as needed (pro re nata)
QD	once a day
QTc	corrected QT
QTcF	Fridericia-corrected QT interval
RA	rheumatoid arthritis
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SJC	swollen joint count
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
ULN	upper limit of normal
VAS	visual analog scale

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APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-763: ABBV-105, Given Alone or in Combination with Upadacitinib (ABBV-599), in Adult Subjects with Active Rheumatoid Arthritis Who Have Completed a Preceding Phase 2 Randomized Controlled Trial

Protocol Date: 06 February 2020

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

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APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Immunology
		Clinical Program Development
		Study Project Management
		Data and Statistical Sciences
		Data and Statistical Sciences
		Clinical Pharmacology and Pharmacometrics
		Medical Writing

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APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the 8 subject encounters. The individual activities are described in detail in the **Operations Manual**.

	LTE Baseline/ Week 12*	Week 18	Week 24	Week 30	Week 36	Week 48	Week 60/PD	Follow-up call (30 days after last dose)
		± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	
Subject information and informed consent	✓							
Eligibility criteria	✓							
Medical and surgical history	✓							
Prior/concomitant therapy	✓*	✓	✓	✓	✓	✓	✓	✓
AE assessment		✓	✓	✓	✓	✓	✓	✓
Patient Questionnaires: • Patient's Assessment of Pain (VAS) • PtGA • HAQ-DI • Morning Stiffness	✓*	✓	✓	✓	✓	✓	✓	
TJC68/SJC66	✓*	✓	✓	✓	✓	✓	✓	
PhGA	✓*	✓	✓	✓	✓	✓	✓	
12-lead ECG	✓*	✓	✓	✓	✓	✓	✓	
Body weight	✓*	✓	✓	✓	✓	✓	✓	
Vital signs	✓*	✓	✓	✓	✓	✓	✓	
Physical exam	✓*	✓	✓	✓	✓	✓	✓	
Local urine pregnancy test (for all female subjects of childbearing potential)	✓*	✓	✓	✓	✓	✓	✓	
Dispense urine pregnancy tests for monthly home testing	✓	✓	✓	✓	✓	✓		
Local laboratory test - Erythrocyte sedimentation rate (ESR)	✓*	✓	✓	✓	✓	✓	✓	

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	LTE Baseline/ Week 12*	Week 18	Week 24	Week 30	Week 36	Week 48	Week 60/PD	Follow-up call (30 days after last dose)
		± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	
Central laboratory tests: • Hematology • Blood chemistry • Urinalysis • hsCRP	✓*	✓	✓	✓	✓	✓	✓	
Central laboratory test - TB screen (QuantiFERON-TB Gold test or interferon gamma release assay [IGRA] equivalent and/or local purified protein derivative [PPD] skin test) or T SPOT®.TB test**						✓		
Optional biomarker sample: Whole blood (serum, plasma, RNA, and DNA)	✓*		✓			✓		
Drug assignment	✓							
Dispense study drug and subject dosing diary	✓*		✓		✓	✓		
Review study drug returned and perform drug reconciliation	✓*	✓	✓	✓	✓	✓	✓	
Reminder to subjects to perform their weekly at-home temperature monitoring***	✓*	✓	✓	✓	✓	✓	✓	

* Tests/study activities are only to be performed if not done as part of Study M16-063.

** As available and if compliant with local TB guidelines (Canada only).

*** As described in Section 6.2.

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APPENDIX E. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Previous Protocol Version

Protocol	Date
Version 1.0	06 August 2018
Version 1.1 (Canada Only)	12 October 2018
Version 2.0	12 October 2018
Version 2.1 (VHP)	17 December 2018
Version 3.0	17 January 2019

- Added CDAI efficacy endpoints to Section 3.2.

  Rationale: *To add endpoints that use a disease activity index that is not influenced by CRP, who's synthesis by the liver is directly blocked by JAK inhibition.*

- Added further detail to Eligibility Criterion 2j in Section 5.1.

  Rationale: *To clarify proper birth control practices that are to be followed during the study.*

- Removed "relative to baseline from Study M16-063" from discontinuation criteria around worsening of SJC and/or TJC, subjects failing to achieve at least 20% improvement in SJC and TJC starting at Week 18, and subjects who fail to achieve CDAI ≤ 10 starting at Week 18 (Section 5.5).

  Rationale: *To clarify discontinuation criteria.*

- Added further detail to study drug discontinuation instructions in Section 5.6.

  Rationale: *To ensure study drug discontinuation processes are clear.*

- Added clarification to the study drug dispensation instructions in Section 5.7.

  Rationale: *To ensure that study drug is properly dispensed.*

- Added information around the Safety Analysis set to Section 7.2 and Section 7.4.

  Rationale: *To clarify the Safety Analysis Set parameters.*

- Added an All ABBV-599 efficacy analysis set and clarifying language in Section 7.3.

  Rationale: *To run an efficacy analysis on all subjects who received study drug.*

- Added an Interim Analysis (Section 7.5).

  Rationale: *To explain the planned, unblinded interim analysis that will be conducted after the Study M16-063 Week 12 database lock.*

- Removed Troponin and Troponin + CK MB testing from Section 3.11 of the Operations Manual (Protocol Appendix F).

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Rationale: *Asymptomatic CPK elevation is a known JAK inhibitor class effect and is described in the Rinvoq USPI and SmPC. Testing asymptomatic subjects with more specific tests designed only for those with suspicion for myocardial infarction (CK-MB and troponin is not warranted and may lead to unnecessary cardiac evaluations and patient anxiety).*

- Added clarification around which type of herpes zoster vaccine the instructions are referring to in Section 3.11 of the Operations Manual (Protocol Appendix F).
  Rationale: *To ensure it's understood that this requirement only applies to those taking a live herpes zoster vaccine.*
- Remove reference to liver biopsies from Section 4.1 of the Operations Manual (Protocol Appendix F).
  Rationale: *To clarify that there are no liver biopsies at Screening or any time during the Study.*

In addition to these modifications, the Amendment contains the following minor changes:

Update Section 2.1 to align with current upadacitinib development program.

Update wording in Section 2.1 and Section 2.2 for clarity.

Update wording in Section 3.3 to clarify that separate DMC and CAC charters have been prepared outside of the protocol.

Update wording around study drug discontinuation in Section 6.2 for clarity.

Update Sponsor/Emergency Medical Contact throughout.

Update to protocol signatories (Appendix C, List of Protocol Signatories).

Added Appendix F to align with the updated AbbVie Protocol template.

Update abbreviations throughout for consistency.

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APPENDIX F. OPERATIONS MANUAL

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